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Henry, R.M.A.; Kamp, O.; Kostense, P.J.; Spijkerman, A.M.; Dekker, J.M.; Nijpels, M.G.A.A.M.; Heine, R.J.; Bouter, L.M.; Stehouwer, C.D.A.

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Mild renal insufficiency is associated with increased left ventricular mass in men, but not in women: An arterial stiffness–related phenomenon—The Hoorn Study

RONALD M.A. HENRY, OTTO KAMP, PIET J. KOSTENSE, ANNEMIEKE M.W. SPIJKERMAN, JACQUELINE M. DEKKER, GIEL NIJPELS, ROBERT J. HEINE, LEX M. BOUTER, and COEN D.A. STEHOUWER

Institute for Research in Extramural Medicine; Institute for Cardiovascular Research; Department of Clinical Epidemiology and Biostatistics; Department of Cardiology; Department of Endocrinology; Department of Internal Medicine, Vrije Universiteit Medisch Centrum, Amsterdam, The Netherlands; and Department of Internal Medicine, University Hospital Maastricht, Maastricht, The Netherlands

Mild renal insufficiency is associated with increased left ventricular mass in men, but not in women: An arterial stiffness–related phenomenon—The Hoorn Study.

Background. Mild renal insufficiency has recently been recognized as an important risk factor for cardiovascular disease (CVD). The mechanisms underlying this association are incompletely understood. Increased left ventricular mass (LVM) is an independent risk factor for CVD, which is particularly common in end-stage renal disease (ESRD) and which has been shown to be associated with mild renal insufficiency. Increased arterial stiffness has also been shown to be an independent risk factor for CVD in ESRD and has also been associated with mild renal insufficiency. We hypothesized that the association between mild renal insufficiency and increased LVM could be mediated through increased arterial stiffness, and that this may be one of the pathways linking mild renal insufficiency to CVD. We therefore investigated, in a cross-sectional population-based study, the influence of increased arterial stiffness on the association between renal function and LVM.

Methods. The study population consisted of 742 elderly individuals (373 men and 369 women). Renal function was estimated by the serum creatinine level in μmol/L; by the Cockcroft-Gault formula in mL/min and by the Modification of Diet in Renal Disease (MDRD) formula. LVM was obtained by echocardiography.

Results. The mean estimates of renal function in men and women were, respectively, 103.7 (SD 17.0) and 86.8 (SD 11.2) μmol/L for the serum creatinine level; 63.4 (SD 12.9) and 61.4 (SD 11.0) mL/min/1.73 m^2 for the Cockcroft-Gault formula; and 59.7 (SD 10.8) and 60.9 (SD 10.5) mL/min per 1.73 m^2 for the MDRD formula. LVM was 93.1 (SD 26.4) g/m^2 in men and 86.7 (SD 22.3) g/m^2 in women. In men, impaired renal function, as estimated by the Cockcroft-Gault and the MDRD formula, was significantly associated with greater LVM after adjustment for age, glucose tolerance, hypertension, and prior CVD [regression coefficient β (95% CI), 1.28 (0.22 to 2.33) g/m^2 and 1.63 (0.41 to 2.86) g/m^2 per 5 mL/min/1.73 m^2 decrease, respectively]. However, the association between impaired renal function and increased LVM was not statistically significant after adjustment for arterial stiffness estimates [regression coefficient β (95% CI), 0.02 (−1.60 to 1.64) g/m^2 and 0.54 (−1.25 to 2.33) g/m^2 per 5 mL/min/1.73 m^2 decrease, respectively]. In women, impaired renal function was not significantly associated with greater LVM.

Conclusion. Our study shows that in a general elderly population, even mild impairment of renal function is associated with adverse changes in left ventricular structure. In men, but not in women, this leads to greater LVM, a process that may be related to increases in arterial stiffness. Importantly, these novel findings suggest that such changes occur early in the process of renal functional deterioration, which may explain, in part, the increase in cardiovascular risk in men with mildly impaired renal function.

Key words: renal function, general population, risk factors, left ventricular hypertrophy.

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Mild renal insufficiency has recently been recognized as an important risk factor for cardiovascular disease (CVD) and mortality [1–4]. The mechanisms underlying this association are incompletely understood. In a previous study, we have shown that a decrease in glomerular filtration rate (GFR) from 90 to 60 mL/min/1.73 m^2 in a population-based setting was associated with a fourfold increase in risk of cardiovascular mortality, and that this was independent of both traditional risk factors (e.g., hypertension and prior cardiovascular disease) and nontraditional risk factors (e.g., markers of endothelial dysfunction and chronic, low-grade inflammation, and homocysteine level) [3].

Increased left ventricular mass (LVM) is an independent risk factor for CVD, which is particularly common in end-stage renal disease (ESRD) and which has been shown to be associated with mild renal insufficiency [1, 5–9]. Increased LVM is thought to increase CVD risk

through a series of unfavorable metabolic, functional, and structural cardiac changes [10–13], thus increasing the risk of myocardial infarction, heart failure, ventricular arrhythmia, and sudden death [8].

Increased arterial stiffness has also been shown to be an independent risk factor for CVD in ESRD and has been shown to be associated mild renal insufficiency [14–19]. Increased arterial stiffness could lead to increased CVD morbidity and mortality via similar phenomena as increased LVM. However, the influence of increased arterial stiffness on the association between mild renal insufficiency and increased LVM has not been investigated. We hypothesized that the association between mild renal insufficiency and increased LVM could be mediated through increased arterial stiffness, and that this may be one of the pathways linking mild renal insufficiency to cardiovascular morbidity and mortality. To test this hypothesis, we investigated, in a cross-sectional population-based cohort of 742 individuals, the association between renal function [as estimated from serum creatinine, the Cockcroft-Gault formula, and the Modification of Diet in Renal Disease (MDRD) formula [3, 20]] and LVM. In addition, we explored whether any such associations could be explained by, on the one hand, traditional CVD risk factors, such as hypertension, or on the other hand, by increased arterial stiffness, a novel risk factor for CVD, which often accompanies impaired renal function [14–19].

METHODS

Study population

For the present cross-sectional investigation, we used data from the 2000 Hoorn Study follow-up examination [21, 22] and the Hoorn Screening Study [23]. Details and sampling procedures have been detailed elsewhere [22, 23]. Briefly, the Hoorn Study is a cohort study of glucose tolerance in the general population ($N = 2484$), which started in 1989 [21]. In 2000, a follow-up examination was carried out among all participants who had given their permission to be recontacted. We invited all those who were diagnosed as having diabetes at the previous 1996 follow-up examination ($N = 176$) and random samples of individuals with normal glucose metabolism ($N = 705$) and impaired glucose metabolism ($N = 193$). Of the 1074 individuals thus invited, 648 (60%) participated. In addition, we invited 217 individuals with diabetes mellitus type 2 from the Hoorn Screening Study, a population-based targeted type 2 diabetes screening study [23], of whom 188 (87%) participated. Among the 455 nonparticipants (53% women), 13% were complete nonresponders. The remaining nonparticipants gave, by telephone interview, various reasons not to participate: lack of interest (30%), comorbidity (23%), age (7%), unwillingness to travel (6%), participation too time-consuming (6%), and miscellaneous reasons (15%).

The local ethics committee approved the study and written informed consent was obtained from all participants. Each participant underwent an oral glucose tolerance test, except those with previously diagnosed diabetes ($N = 67$), and was classified according to the 1999 World Health Organization (WHO) criteria [24]. The final study population consisted of 822 individuals (290 with normal glucose metabolism, 187 with intermediate glucose metabolism, and 345 with type 2 diabetes mellitus), as data on 14 individuals were missing.

Estimates of renal function

Renal function was estimated by the serum creatinine level in μmol/L; by the Cockcroft-Gault formula in mL/min ([140 – age] * body weight/[creatinine * 72] * 0.85 if female); and by the MDRD formula (Levey's equation) in mL/min ($170 * [\text{creatinine}]^{-0.999} * [\text{age}]^{-0.176} * [\text{urea}]^{-0.170} * [\text{albumin}]^{+0.318} * 0.762$ if female) [13]. The Cockroft-Gault and MDRD formulas were both expressed per 1.73 m^2 body surface area [25]. Formulas are given in traditional units. To convert to International System units multiply creatinine in mg/dL by 88.4, urea in mg/dL by 0.357, and albumin in g/dL by 10.

Echocardiography

An experienced research technician unaware of the participants' clinical or glucose tolerance status obtained an echocardiogram in each participant, according to a standardized protocol, with the use of a single ultrasound scanner (HP SONOS 5500) (Andover, MA, USA). M-mode recordings were digitally stored and read according to the guidelines of the American Society of Echocardiography [26, 27].

Left ventricular end-diastolic diameter (EDD), posterior wall thickness (PWT), and the interventricular septum thickness (IVS) were measured at end diastole. LVM was calculated as 0.8 (1.04) $[(\text{EDD} + \text{IVS} + \text{PWT})^3 - \text{EDD}^3] + 0.6$ divided by body surface area in g/m^2 and relative wall thickness (RWT) as (IVS + PWT)/EDD [27]. Each echocardiogram was inspected afterwards by a senior cardiologist blinded to the participants' clinical or glucose tolerance status to monitor the quality of both recordings and readings.

Left ventricular geometric patterns were classified according to Heesen et al [28].

Arterial stiffness

We measured carotid and femoral artery distensibility and compliance coefficients; total systemic arterial compliance; the height-adjusted carotid-femoral transit

time, a surrogate for carotid-femoral pulse wave velocity (PWV); and the aortic augmentation index, as previously described in detail [22, 29]. The distensibility and compliance coefficient reflect elastic properties and buffering capacity, respectively [30]. Total systemic arterial compliance reflects the overall buffering capacity of the arterial system, mainly of the proximal aorta [29]. Carotid-femoral transit time estimates the average aortic distensibility or bulk modulus K ($K = PWV^2 (\rho$, where ρ is blood viscosity). This method assumes a uniform aorta and gives compliance of mainly the descending aorta. The aortic augmentation index depends on timing of the reflected waves, and thus on PWV, as well as on the magnitude and location of reflection sites, and is therefore a less pure estimate of arterial stiffness [29].

Other measurements

Health status, medical history, current medication use, and smoking habits were assessed by a questionnaire [21, 23]. We determined systolic and diastolic pressure, mean arterial pressure, pulse pressure, hypertension (defined as systolic pressure $\geq$ 140 mm Hg and diastolic pressure $\geq$ 90 mm Hg and/or the current use of antihypertensive medication), glucose, glycated hemoglobin, insulin, homocysteine, serum total, high-density and low-density-lipoprotein cholesterol, serum triglycerides, body mass index, waist-to-hip ratio, and ankle-brachial pressure index as described elsewhere [22, 23, 31].

Resting electrocardiograms were automatically coded according to the Minnesota Code [32]. Prior CVD was defined as Minnesota Code 1.1-1.3, 4.1-4.3, 5.1-5.3, or 7.1 on the electrocardiogram or coronary bypass operation or angioplasty, or an ankle-brachial blood pressure index <0.9 in either leg, or peripheral arterial bypass, or amputation for atherosclerotic disease.

Statistical analyses

All analyses were performed using SPSS 10.1 for Windows 98. We used multiple linear regression analysis to investigate the associations between the estimates of renal function (determinants) and left ventricular structure (outcomes). All associations were first analyzed without adjustments (crude model) and then with adjustment for potential confounders (adjusted models). We analyzed men and women separately, because there may be important gender differences in the determinants of LVM [33–37]. Statistically this gender difference was confirmed by the results of our interaction analyses (gender * estimate of renal function) in which all interaction terms were $\leq$ 0.005. As left ventricular structure is known to be affected by age and glucose tolerance status [38–42], these variables were considered first in the adjusted models (age was omitted from the models with the Cockcroft-Gault and MDRD formula because of its incorporation in both formulas). We then added potential confounding or mediating variables to the models [i.e., hypertension, prior cardiovascular disease, (micro-) albuminuria, homocysteine, and arterial compliance). Results are described as regression coefficients (β) with 95% CI per a 5 unit increase for serum creatinine level and per a 5 unit decrease for both the Cockcroft-Gault and MDRD formula.

Diabetes and hypertension are often accompanied by impaired renal function. We therefore used interaction terms to investigate whether the association between estimates of renal function and left ventricular structure differed according to the presence of diabetes and hypertension, because any such interactions might be clinically important.

P values < 0.05 were considered statistically significant, except for the interaction analyses where we used < 0.10 as cutoff value.

RESULTS

In 42 of the 822 participants, LVM could not be determined due to either a high body mass index ($N = 33$; body mass index of those with qualitatively satisfactory examinations versus those without, 27.5 $\pm$ 3.8 kg/m^2 versus 37.9 $\pm$ 8.9 kg/m^2 ($P < 0.001$) or a poor transthoracic window ($N = 9$). In the remaining 780 individuals all three estimates of renal function could be determined in 742 individuals because of (randomly) missing laboratory values.

Clinical characteristics

The mean serum creatinine level was 103.7 (SD 17.0) μmol/L in men and 86.8 (SD 11.2) μmol/L in women (Table 1). Mean creatinine clearance, as estimated by the Cockcroft-Gault formula, was 63.4 (SD 12.9) mL/min/1.73 m^2 in men and 61.4 (SD 11.0) mL/min/ 1.73 m^2 in women. Mean glomerular filtration rate (GFR), as estimated by the MDRD formula, was 59.7 (SD 10.8) mL/min per 1.73 m^2 in men and 60.9 (SD 10.5) mL/min per 1.73 m^2 in women. LVM was 93.1 (SD 26.4) g/m^2 in men and 86.7 (SD 22.3) g/m^2 in women.

Associations between estimates of renal function and LVM

In men, impaired renal function, as estimated by the Cockcroft-Gault and the MDRD formula, was significantly associated with greater LVM after adjustment for age, glucose tolerance, hypertension and prior cardiovascular disease (regression coefficient β (95% CI), 1.28 (0.22 to 2.33) g/m^2 and 1.63 (0.41 to 2.86) g/m^2 per 5 mL/min/1.73 m^2 decrease, respectively (Table 2, model 4). Additional adjustment for (micro-) albuminuria or

Table 1. Clinical characteristics of the study population

	Men ($N = 373$)	Women ($N = 369$)
Age *years*	68.2 ± 7.3	69.1 ± 6.7
Fasting glucose *mmol/L*	6.5 ± 1.6	6.4 ± 1.4
Postload glucose *mmol/L*	7.0 ± 2.6	7.3 ± 2.6
Glycated hemoglobin%	6.1 ± 0.8	6.1 ± 0.7
Fasting insulin *pmol/L*	59.5 (43.0–85.0)	61.0 (43.0-91)
Body mass index kg/m^2	27.3 ± 3.3	27.6 ± 4.0
Waist-to-hip ratio	0.98 ± 0.07	0.88 ± 0.09[a]
Total cholesterol *mmol/L*	5.4 ± 1.0	6.0 ± 1.0[a]
Low-density lipoprotein cholesterol *mmol/L*	3.4 ± 0.9	3.8 ± 0.9[a]
High-density lipoprotein cholesterol *mmol/L*	1.2 ± 0.3	1.6 ± 0.4[a]
Triglycerides *mmol/L*	1.3 (1.0–1.9)	1.3 (1.0-1.8)
Lipid-lowering medication%	18	15
Systolic pressure *mm Hg*	140 ± 17	146 ± 22[a]
Diastolic pressure *mm Hg*	78 ± 9	77 ± 9
Mean arterial pressure *mm Hg*	99 ± 11	100 ± 13
Hypertension%	68	70
Antihypertensive medication%	36	40
Arterial stiffness		
Carotid distensibility $10^{-3}.kPa^{-1}$	12.1 ± 4.3	11.0 ± 4.5[a]
Carotid compliance $mm^2.kPa^{-1}$	0.64 ± 0.24	0.48 ± 0.17[a]
Femoral distensibility $10^{-3}.kPa^{-1}$	4.6 ± 2.1	4.8 ± 2.2
Femoral compliance $mm^2.kPa^{-1}$	0.40 ± 0.20	0.33 ± 0.40[a]
Carotid-femoral transit time[b] *msec*	56.8 ± 16.9	51.7 ± 15.1[a]
Total systemic arterial compliance *mL/mm Hg*	0.90 ± 0.29	1.16 ± 0.32[a]
Aortic augmentation index%	29.8 ± 8.9	35.5 ± 7.4[a]
Prior cardiovascular disease%	47	48
Smoking%	18	12[a]
(Micro-) albuminuria%	17	12[a]
Homocysteine μ*mol/L*	12.4 ± 4.51	11.0 ± 3.41[a]
Renal function estimate		
Serum creatinine level μ*mol/L*	103.7 ± 17.0	86.8 ± 11.2[a]
Cockcroft-Gault formula *mL/min/1.73 m²*	63.4 ± 12.9	61.4 ± 11.0[a]
MDRD formula (GFR) *mL/min/1.73 m²*	59.7 ± 10.8	60.9 ± 10.5[c]
Measurements of left ventricular structure		
Mass g/m^2	93.1 ± 26.4	86.7 ± 22.3[a]
End diastolic diameter *cm*	5.24 ± 0.59	4.90 ± 0.52[a]
Posterior wall thickness *cm*	0.93 ± 0.15	0.88 ± 0.15[a]
Interventricular septum thickness *cm*	1.01 ± 0.24	0.96 ± 0.23[a]
Relative wall thickness	0.38 ± 0.09	0.38 ± 0.09

MDRD is Modification of Diet in Renal Disease; GFR is glomerular filtration rate. Results are expressed as mean ± standard deviation, percentage or median (interquartile range). Measurements of left ventricular structure were derived from M-mode.

[a] *P* value for difference < 0.05.

[b] Adjusted for height; available in 151 in men and 148 women. Total systemic arterial compliance as estimated by statistical values divided by local pulse pressure (see the **Methods** section).

[c] *P* value for difference < 0.1.

homocysteine somewhat decreased the associations (Table 2, models 5 and 6, respectively). However, the association between impaired renal function and increased LVM decreased substantially, and was not statistically significant, after adjustment for arterial stiffness estimates (Table 2, models 7b to d). In women, impaired renal function was not significantly associated with greater LVM (Table 2, models 1 to 6). The *P* values for interaction (gender * estimate of renal function) were ≤ 0.005.

Renal function and left ventricular structure and geometry

Table 3 and Figure 1 show that the percentage of men with normal left ventricular geometry decreased significantly with lower GFR, whereas the percentage of men with left ventricular remodeling or hypertrophy increased significantly [*P* value for overall linear-by-linear association over categories of GFR and left ventricular geometric patter ($N = 0.002$)].

In women, lower GFR was not significantly associated with left ventricular geometry (Table 3) [*P* value for overall linear-by-linear association over categories of GFR and left ventricular geometric patter ($N = 0.51$)].

Table 2 shows that, in men, impaired renal function was significantly associated with greater LVM, but does not provide insight into the role of the individual elements of the formula for LVM. Table 4 shows that, after adjustment for age, glucose tolerance, hypertension, prior CVD and (micro-) albuminuria, lower GFR was significantly associated with greater PWT [β per 5 mL/min/1.73 m^2 decrease, 0.014 cm (0.004 to 0.024)], IVS [β, 0.024 cm (0.014 to 0.033)], and RWT [β, 0.007 (0.002 to 0.011)]. In women a similar pattern was seen. Further analyses showed that the correlation coefficient between PWT and IVS was 0.71 in men and 0.51 in women (*P* value for both < 0.001). This difference may explain why the associations between lower GFR and altered left ventricular structure were similar in men and women (Table 4), while the association between lower GFR and greater LVM was seen only in men (Table 2).

Additional analyses

Additional adjustment for body mass index, waist-to-hip ratio, insulin, lipid profile, smoking, heart rate, or the use of lipid-lowering or antihypertensive medication [including angiotensin-converting enzyme (ACE) inhibitors] did not materially alter our results stiffness (data not shown). Results were also not materially altered if we repeated the analyses with any of the other measurements of arterial stiffness (data not shown). Results were not altered if we excluded individuals with left ventricular wall motion abnormalities ($N = 49$) (11 women) and/or those with GFR < 30 mL/min1.73 m^2 as estimated by the MDRD formula ($N = 5$) (2 women). In addition, these results did not differ according to the presence of hypertension or diabetes (*P* values for interaction both > 0.16) (data not shown).

Table 2. Associations between estimates of renal function and left ventricular mass in men and women

	Dependent Variable Left ventricular mass g/m^2	Men			Women		
		Serum creatinine level	Cockcroft-Gault formula[a]	MDRD formula[a]	Serum creatinine level	Cockcroft-Gault formula[a]	MDRD formula[a]
Model	Added Variables						
1	Crude	1.05 (0.26; 1.84)	1.58 (0.53; 2.62)	1.98 (0.72; 3.24)	0.40 (−0.63; 1.43)	0.75 (−0.32; 1.82)	0.23 (−0.87; 1.33)
2	1 + age + glucose tolerance	0.68 (−0.12; 1.48)	1.75 (0.67; 2.82)	1.97 (0.69; 3.24)	0.16 (−0.85; 1.17)	1.01 (−0.06; 2.08)	0.14 (−0.96; 1.24)
3	2 + hypertension	0.65 (−0.14; 1.43)	1.54 (0.49; 2.58)	1.64 (0.40; 2.88)	0.06 (−0.95; 1.07)	0.99 (−0.07; 2.05)	−0.06 (−1.15; 1.04)
4	3 + prior cardiovascular disease	0.62 (−0.16; 1.40)	1.28 (0.22; 2.33)	1.63 (0.41; 2.86)	−0.09 (−1.09; 0.91)	0.75 (−0.31; 1.81)	−0.14 (−1.22; 0.94)
5	3 + (b = micro-) albuminuria	0.49 (−0.30; 1.29)	1.00 (−0.09; 2.08)	1.39 (0.16; 2.62)	0.02 (−0.97; 1.01)	0.81 (−0.23; 1.85)	0.02 (−1.05; 1.09)
6	3 + homocysteine	0.68 (−0.13; 1.49)	1.31 (0.16; 2.46)	1.51 (0.26; 2.75)	−0.32 (−0.14; 0.76)	0.58 (−0.52; 1.68)	−0.63 (−1.77; 0.51)
7a	2 + mean arterial pressure	—	1.59 (0.56; 2.61)	1.76 (0.54; 2.98)	—	—	—
7b	6a + carotid distensibility	—	1.18 (0.14; 2.21)	1.32 (0.12; 2.51)	—	—	—
7c[b]	6a + carotid-femoral transit time	—	0.02 (−1.60; 1.64)	0.54 (−1.25; 2.33)	—	—	—
7d[b]	6a + carotid Distensibility + carotid-femoral transit time	—	–	0.12 (−1.66; 1.89)	—	—	—

Results are expressed as regression coefficients and their 95% CI. Serum creatinine level expressed per 5 μmol/L increase, Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) formula expressed per 5 mL/min/1.73 m^2 decrease.

[a] In adjusted models (2 to 7), age was omitted, as this variable is included in the formula. Results were similar when model 4 was additionally adjusted for lipid profile, smoking or waist-to-hip ratio.

[b] Additionally adjusted for height; number of men = 151 as carotid-femoral transit time was available in a random subsample only.

Table 3. Gender-specific characteristics of left ventricular geometry according to glomerular filtration rate (GFR)

	Men[a]			Women[a]		
Left ventricular geometry	GFR ≥ 70	50 ≤ GFR < 70	GFR < 50	GFR ≥ 70	50 ≤ GFR < 70	GFR < 50
Normal geometry%	82.5	76.9	60.9	76.5	81.3	75.0
Concentric remodeling%	10.5	11.7	15.9	13.2	12.8	18.2
Eccentric hypertrophy%	1.8	6.9	10.1	5.9	2.7	6.8
Concentric hypertrophy%	5.3	4.5	13.0	4.4	3.1	—

Left ventricular geometric patterns within each category of GFR according to the Modification of Diet in Renal Diseae (MDRD) formula in mL/min/1.73 m^2 (see the **Methods** section).

[a] *P* value for linear-by-linear association = 0.002 in men and = 0.51 in women.

DISCUSSION

The present population-based study of renal function and left ventricular structure had three main findings. First, impairment of renal function was associated with greater left ventricular EDD and PWT and IVS, which together determine LVM and left ventricular geometry. Second, because PWT and IVS were more closely related to each other in men than in women, impairment of renal function was associated with significantly greater LVM and abnormal left ventricular geometry only in men. Third, the association between impairment of renal function and greater LVM in men was explained entirely by a greater arterial stiffness in men with impaired renal function.

In men, a decrease in MDRD-estimated GFR from 90 to 60 mL/min/1.73 m^2 was associated with an 8.3 g/m^2 greater LVM (i.e., a 9% increase as compared to the male population mean). Greater LVM may increase the risk of myocardial infarction, heart failure, ventricular arrhythmia, and sudden death [7, 8, 40, 43], and may thus present a link between mild impairment of renal function and increased risk of CVD [1, 4, 6, 9]. However, additional studies are required to directly test this hypothesis.

This population-based study extends previous investigations [44–50], most of which have been relatively small [45–47], and/or have focused upon selected populations[44, 48–50].

In contrast to previous studies [45–47], we found impaired renal function to be associated with greater LVM in men but not in women. There may be two explanations for this finding. First, we studied an elderly population, and selective mortality of women with greater LVM may have weakened the association between renal function and LVM ("healthy survivor effect"). Indeed, a greater

Table 4. Associations between glomerular filtration rate and left ventricular structure in men and women

Model	Dependent variable	Men	Women
1	End diastolic diameter *cm*	0.012 (−0.017; 0.042)	0.010 (−0.020; 0.039)
2	Posterior wall thickness *cm*	0.014 (0.014; 0.024)	0.011 (0.001; 0.020)
3	Interventricular septum thickness *cm*	0.024 (0.014; 0.033)	0.017 (0.007; 0.027)
4	Relative wall thickness	0.007 (0.002; 0.011)	0.006 (0.001; 0.010)

Results are expressed as regression coefficients and their 95% CI per 5 mL/min/1.7 3 m^2 decrease as estimated by the Modification of Diet in Renal Disease (MDRD) formula (see the **Methods** section). All models adjusted for age, glucose tolerance, hypertension, prior cardiovascular disease, and (micro-) albuminuria.

LVM is thought to be more strongly associated with risk of CVD in women than in men [33–35, 37, 51]. Second, we observed a stronger correlation between PWT and IVS in men than in women, in whom changes in cardiac structure thus seemed less coordinated. This apparent lack of coordination may reflect a gender0000-specific cellular and biochemical response to myocyte growth-promoting stimuli [35, 51–53]. In this context, it must be emphasized that the lack of an association between renal function and LVM in women does not necessarily mean that the cardiac changes associated with renal function impairment in women are innocuous. In women with impaired renal function, greater left ventricular end diastolic diameter and PWT and IVS may increase risk of cardiac events even without increasing LVM, but data on this issue are scarce/and this hypothesis needs further testing [51, 54].

The association between mild renal insufficiency and greater LVM in men was accounted for entirely by greater arterial stiffness in men with mild renal insufficiency. The most straightforward explanation for this finding is that mild renal insufficiency increases arterial stiffness, which in turn leads to an increase in LVM [14–17, 55–57]. Indeed, there is much evidence in favor of this interpretation [4]. The important new finding in this study is that this process seems to start very early in the course of renal functional deterioration.

This study had several limitations. First, we cannot exclude that some unmeasured variable confounded the associations between renal function and left ventricular structure (in other words, we can not exclude the possibility that the increase in LVM and arterial stiffness with deteriorating GFR is the consequence of an unknown risk factor causing both). However, we extensively characterized out population (Table 1), and we can reasonably exclude that variables typically associated with impaired renal function, such as hypertension, hyperinsulinemia, and glucose intolerance, confounded the results. Second, our study was cross-sectional. Our inference that impaired renal function increases arterial stiffness and thus LVM is therefore uncertain. We cannot exclude that some unmeasured variable simultaneously increases arterial stiffness and LVM without these increases being causally related, and longitudinal studies are required to investigate this.

We conclude that, in a general elderly population, even mild impairment of renal function is associated with adverse changes in left ventricular structure. In men, but not in women, this leads to greater LVM and abnormal left ventricular geometry, processes that may be related to increases in arterial stiffness. Importantly, such changes occur early in the process of renal functional deterioration. Whether such changes can explain, in part, the increase in cardiovascular risk in individuals with mildly impaired renal function remains to be shown.

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Reprint requests to Professor Coen D.A. Stehouwer, M.D., Ph.D., Department of Internal Medicine, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands.
E-mail: csteh@sint.azm.nl

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